Claims 60-62, 64-72, and 74-106 are pending in the instant application and presented for examination. Claims 81-106 are newly added. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." Applicants respectfully note that pending claim 64 was inadvertently left off the Examiner's Office Action Summary dated May 29, 2002. Reconsideration is respectfully requested.

Support for new claims 81, 91, and 102-104, is found, for example, in claims 60 and 70 and on page 8, line 9. Support for new claims 82-90 is found, for example, in claims 61-69, respectively. Support for new claims 91-101 is found, for example, in claims 71-80, respectively. Support for new claims 105 and 106 is found, for example, on page 8, line 9.

In view of the forgoing support, Applicants respectfully request that the new claims be entered.

I. Rejection under 35 U.S.C. 112, second paragraph

Claims 60-62, 64-72 and 74-80 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. According to the Office Action, the use of the term "low" is indefinite. In response, Applicants respectfully traverse the rejection.

Claim 60 reads as follows:

> 60. A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction comprising administering to a subject in need of prostaglandin at least one NO producing agent at a low dose which does not produce significant systemic side effects but which decreases pain associated with prostaglandin use.

Claim 60 clearly sets forth that the low dose is a dose which does not produce significant systemic side effects, but decreases pain associated with prostaglandin use. Furthermore, examples of low dose amounts for various NO producing agents are provided throughout the specification (*see, for example*, page 8, line 11, and page 15, lines 10-17 of the

specification). Those of ordinary skill in the art would know or could easily ascertain by, for example, dose titration, amounts of NO producing agents which do not produce significant systemic side effects. Systemic side effects include, among other effects, a drop in blood pressure, headache, and direct modulation of the erectile response by directly causing vascular smooth muscle relaxation such that there is an immediate erectile response independent of a natural sexual signal from the brain. As the term "low dose" is clearly defined in the claims, Applicants respectfully request that the rejection be withdrawn.

II. Rejection under 35 U.S.C. § 102(e)

Claims 60, 61, 66-71 and 77-80 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,849,803 ("the '803 patent"). The Examiner states that the '803 patent does not teach or suggest that 0.5-1.5 mg of nitroglycerin would cause systemic side effects, and thus the amount of nitroglycerine would meet the features of the current claims. In response, Applicants respectfully traverse the rejection.

The '803 patent teaches administration of large doses (e.g., 0.5 to 5 mg) of nitroglycerin to treat erectile dysfunction. The '803 patent discloses that such doses are very high compared to the dose of nitroglycerin normally given to angina pectoris patients (*see*, col. 3, lines 22-24, the '803 patent). In particular, the '803 patent teaches a dose range of 0.5 to 5 mg, preferably, 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence (*see*, col. 3, lines 20-22 and Table 1 at col. 4, 5 and 6, the '803 patent). The '803 patent teaches that these dosages produce a penile erectile response, and a further systemic effect of a drop in blood pressure (see notes below Table I, columns 5 and 6).

In contrast to the '803 patent, the present invention provides dosages of NO producing agents which are about one half to about one twentieth of those known to induce vasodilation in "normal" circulations. These low doses of NO producing agents

exert no systemic effect in normal vasculature. Treatment with an NO provider according to the present invention does ***not*** directly modulate the erectile response by directly causing vascular smooth muscle relaxation such that there is an immediate erectile response, because the NO producing agent is administered at a dosage which is much *lower* than required to directly effect a systemic response.

For example, Case Nos. 2 and 3 at page 17 of the specification describe application of a Nitropatch delivering nitroglycerin at a rate of 0.2 mg/hour 10 to 20 minutes prior to injection of a PGE1. This dose of nitroglycerin is 7.5- to 15-fold lower than the lowest dose taught or disclosed to be useful by the '803 patent.

Clearly, the '803 patent provides no teaching of administration of an NO producing agent in a low dose which does not cause significant systemic side effects, but which decreases pain associated with prostaglandins. Thus, this reference cannot anticipate the claims currently pending.

As such, withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested.

III. Rejection of Claims 60-80 under 35 U.S.C. § 103(a)

Claims 60-80 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,894,803 in view of Akkus *et al.* (Medline Abstract, AN 95174112) and Cesar *et al.* (WO 94/04120). In response, Applicants respectfully traverse the rejection.

As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

There is simply no teaching or suggestion in the secondary references to modify the teachings of the '803 patent to arrive at the instantly claimed invention. The

'803 patent teaches a dose range of 0.5 to 5 mg, preferably 0.5 to 2.5 mg of nitroglycerin alone or in combination with another agent to treat impotence. There is absolutely no teaching or suggestion of reducing side effects, or reducing the pain of prostaglandin treatment, by using a dose of nitroglycerin which does not produce significant systemic side effects, but decreases pain associated with prostaglandin use, as is currently taught and claimed. Accordingly, this reference fails to teach or suggest all the limitations of the claims currently pending.

The Abstract by Akkus *et al.* is merely a report of an "unusual case" of clitorimegaly wherein intracorporeal injection of prostaglandin E1 resulted in marked clitoral erection. There is no discussion whatsoever of administration of a NO producing agent or an agent that augments cGMP.

WO 94/04120 teaches the use of histamine H2 receptor agonists and/or histamine H3 receptor agonists for treatment of erectile dysfunction in animals, particularly humans. Use of NO producing agents to treat male impotence is discussed in the background section of this reference. The NO producing agent, SIN, is disclosed as being considerably less effective than PGE1 and is taught not to play a role in the management of male impotence. There is no other disclosure of NO producing agents in this reference.

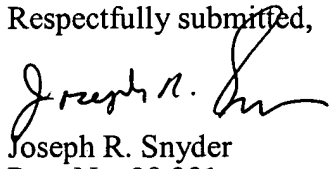
Accordingly, Applicants assert that the secondary references fail to remedy the deficiencies of the primary reference cited in this rejection. The combination of references provides no reasonable expectation of success that administration of a NO producing agent or an agent that augments cGMP at a low dose which does not produce significant side effects would be useful in decreasing the pain associated with prostaglandin administration for erectile dysfunction.

In view of the foregoing, a *prima facie* case of obviousness has not been established. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

IV. Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

New claims 81-106 have been added as follows:

81. (New) A method of decreasing pain associated with the use of prostaglandin in a subject in need thereof, said method comprising:

administering a therapeutically effective amount of prostaglandin and at least one NO producing agent in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one NO producing agent is in a unit dose of 0.67 μmole or less.

82. (New) The method of claims 81, wherein the subject is male.

83. (New) The method of claim 81, wherein the subject is female.

84. (New) The method of claim 81, wherein the NO producing agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

85. (New) The method of claim 81, wherein the NO producing agent inhibits a cyclic nucleotide phosphodiesterase.

86. (New) The method of claim 85, wherein the cyclic nucleotide phosphodiesterase is PDE3.

87. (New) The method of claim 81, wherein the NO producing agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction..

88. (New) The method of claim 81, wherein two agents are administered.

89. (New) The method of claim 81, wherein the NO producing agent is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

90. (New) The method of claim 89, wherein the NO producing agent is glyceryl trinitrate.

91. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of is in a unit dose of 0.67 μmole or less.

92. (New) The method of claim 91, wherein the subject is male.

93. (New) The method of claim 91, wherein the subject is female.

94. (New) The method of claim 91, wherein the agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

95. (New) The method of claim 91, wherein the agent augments action of cGMP by generating CO.

96. (New) The method of claim 91, wherein the agent inhibits a cyclic nucleotide phosphodiesterase.

97. (New) The method of claim 96, wherein the cyclic nucleotide phosphodiesterase is PDE3.

98. (New) The method of claim 91, wherein the agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction.

99. (New) The method of claim 91, wherein two agents are administered.

100. (New) The method of claim 91, wherein said agent which augments action of cGMP is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

101. (New) The method of claim 100, wherein the agent which augments action of cGMP is glyceryl trinitrate.

102. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of 200 μg or less.

103. (New) A method for decreasing pain associated with the presence of prostaglandin, said method comprising:

administering at least one NO producing agent in an amount effective to decrease pain resulting from the presence of prostaglandin, wherein said amount of at least one NO producing is in a unit dose of 200 μg or less.

104. (New) A method for decreasing pain associated with the presence of prostaglandin, said method comprising:

administering at least one NO producing agent in an amount effective to decrease pain resulting from the presence of prostaglandin, wherein said amount of at least one NO producing agent is in a unit dose of 0.67 μmole or less.

105. (New) A method of decreasing pain associated with the use of prostaglandin in a subject in need thereof, said method comprising:

administering a therapeutically effective amount of prostaglandin and at least one NO producing agent in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one NO producing agent is in a unit dose of 200 μg or less.

106. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a male subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of 200 μg or less.

PENDING CLAIMS

60. (Amended) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction comprising administering to a subject in need of prostaglandin at least one NO producing agent at a low dose which does not produce significant systemic side effects but which decreases pain associated with prostaglandin use.

61. The method of claim 60 wherein the subject is male.

62. The method of claim 60 wherein the subject is female.

63. The method of claim 60 wherein the NO producing agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

64. The method of claim 60 wherein the NO producing agent inhibits a cyclic nucleotide phosphodiesterase.

65. The method of claim 64 wherein the cyclic nucleotide phosphodiesterase is PDE3.

66. The method of claim 60 wherein the NO producing agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction.

67. The method of claim 60 wherein two agents are administered.

68. The method of claim 60 wherein the NO producing agent is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

69. The method of claim 60 wherein the NO producing agent is glyceryl trinitrate.

70. (Amended) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction comprising administering to a subject in need of prostaglandin at least one agent at a low dose which does not produce significant systemic side effects but which augments action of cGMP so that pain associated with prostaglandin use sensed by nociceptive tissue in close proximity to engorgeable tissue is decreased.

71. The method of claim 70 wherein the subject is male.

72. The method of claim 70 wherein the subject is female.

73. The method of claim 70 wherein the agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

74. The method of claim 70 wherein the agent augments action of cGMP by generating CO.

75. The method of claim 70 wherein the agent inhibits a cyclic nucleotide phosphodiesterase.

76. The method of claim 75 wherein the cyclic nucleotide phosphodiesterase is PDE3.

77. The method of claim 70 wherein the agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction.

78. The method of claim 70 wherein two agents are administered.

79. The method of claim 70 wherein said agent which augments action of cGMP is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

80. The method of claim 70 wherein the agent which augments action of cGMP is glyceryl trinitrate.

81. (New) A method of decreasing pain associated with the use of prostaglandin in a subject in need thereof, said method comprising:

administering a therapeutically effective amount of prostaglandin and at least one NO producing agent in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one NO producing agent is in a unit dose of 0.67 μmole or less.

82. (New) The method of claims 81, wherein the subject is male.

83. (New) The method of claim 81, wherein the subject is female.

84. (New) The method of claim 81, wherein the NO producing agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

85. (New) The method of claim 81, wherein the NO producing agent inhibits a cyclic nucleotide phosphodiesterase.

86. (New) The method of claim 85, wherein the cyclic nucleotide phosphodiesterase is PDE3.

87. (New) The method of claim 81, wherein the NO producing agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction.

88. (New) The method of claim 81, wherein two agents are administered.

89. (New) The method of claim 81, wherein the NO producing agent is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

90. (New) The method of claim 89, wherein the NO producing agent is glyceryl trinitrate.

91. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of is in a unit dose of 0.67 μmole or less.

92. (New) The method of claim 91, wherein the subject is male.

93. (New) The method of claim 91, wherein the subject is female.

94. (New) The method of claim 91, wherein the agent augments action of cAMP in smooth muscle and reduces action of cAMP in nociceptive tissue.

95. (New)The method of claim 91, wherein the agent augments action of cGMP by generating CO.

96. (New) The method of claim 91, wherein the agent inhibits a cyclic nucleotide phosphodiesterase.

97. (New) The method of claim 96, wherein the cyclic nucleotide phosphodiesterase is PDE3.

98. (New) The method of claim 91, wherein the agent is delivered by a route selected from the group consisting of oral administration, intravenous administration, subcutaneous administration, inhalation or intranasal administration, transdermal application, topical application, rectal administration, intraurethral administration, and intracavernous introduction.

99. (New) The method of claim 91, wherein two agents are administered.

100. (New) The method of claim 91, wherein said agent which augments action of cGMP is selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine, molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, N-hydroxy-L-arginine, S,S-dinitrosodithiol and NO gas.

101. (New) The method of claim 100, wherein the agent which augments action of cGMP is glyceryl trinitrate.

102. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of 200 μg or less.

103. (New) A method for decreasing pain associated with the presence of prostaglandin, said method comprising:

administering at least one NO producing agent in an amount effective to decrease pain resulting from the presence of prostaglandin, wherein said amount of at least one NO producing is in a unit dose of 200 μg or less.

104. (New) A method for decreasing pain associated with the presence of prostaglandin, said method comprising:

administering at least one NO producing agent in an amount effective to decrease pain resulting from the presence of prostaglandin, wherein said amount of at least one NO producing agent is in a unit dose of 0.67 μmole or less.

105. (New) A method of decreasing pain associated with the use of prostaglandin in a subject in need thereof, said method comprising:

administering a therapeutically effective amount of prostaglandin and at least one NO producing agent in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one NO producing agent is in a unit dose of 200 μg or less.

106. (New) A method of decreasing pain associated with use of prostaglandins for treatment of erectile tissue dysfunction, said method comprising:

administering to a male subject in need of prostaglandin at least one agent which augments action of cGMP in an amount effective to decrease pain associated with the use of said prostaglandin, wherein said at least one agent which augments action of cGMP is in a unit dose of 200 μg or less.